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Evaluation of USP Apparatus 3 for Dissolution Testing of Immediate-Release Products

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ABSTRACT We sought to evaluate whether U.S. Pharmacopeia (USP) apparatus 3 can be used as an alternative to USP apparatus 2 for dissolution testing of immediate-release (IR) dosage forms. Highly soluble drugs, metoprolol and ranitidine, and poorly soluble drugs, acyclovir and furosemide, were chosen as model drugs. The dissolution profiles of both innovator and generic IR products were determined using USP apparatus 2 at 50 rpm and apparatus 3 at 5, 15, and 25 dips per minute (dpm). The dissolution profiles from USP apparatus 3 were compared to those from USP apparatus 2 using the f_2 similarity test. The dissolution profile from USP apparatus 3 generally depends on the agitation rate, with a faster agitation rate producing a faster dissolution rate. It was found that USP apparatus 3 at the extreme low end of the possible agitation range, such as 5 dpm, gave hydrodynamic conditions equivalent to USP apparatus 2 at 50 rpm. With appropriate agitation rate, USP apparatus 3 can produce similar dissolution profiles to USP apparatus 2 or distinguish dissolution characteristics for the IR products of metoprolol, ranitidine, and acyclovir. Incomplete dissolution was observed for the furosemide tablets using USP apparatus 3. Although it is primarily designed for the release testing of extended-release products, USP apparatus 3 may be used for the dissolution testing of IR products of highly soluble drugs, such as metoprolol and ranitidine, and some IR products of poorly soluble drugs, such as acyclovir. USP apparatus 3 offers the advantages of avoiding cone formation and mimicking the changes in physiochemical conditions and mechanical forces experienced by products in the gastrointestinal tract.

KEYWORDS: Dissolution, USP apparatus 2, USP apparatus 3, Immediate- Release, and Product.

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INTRODUCTION

The Bio-Dis dissolution apparatus has had a relatively short history since its proposal by Beckett et al[1] and its incorporation into the United States Pharmacopoeia (USP) in 1991[2] as apparatus 3 for drug release testing of extended-release products as an alternative to the basket, USP apparatus 1; and paddle, USP apparatus 2. The development of USP apparatus 3 was based on the recognition of the need to establish in vitro and in vivo correlation and the fact that the dissolution results obtained with USP apparatuses 1 and 2 may be significantly affected by shaft wobble, location, centering, and coning[1] . USP apparatus 3 offers the advantages of mimicking the changes in physiochemical conditions and the mechanical forces experienced by products in the gastrointestinal tract[1] .

The design of USP apparatus 3 is based on the disintegration tester. The assembly of USP apparatus 3[2] consists of a set of cylindrical, flat-bottomed glass outer vessels; a set of glass reciprocating inner cylinders; and stainless steel fittings and screens that are made of suitable material and that are designed to fit the tops and bottoms of the reciprocating cylinders. Operation involves programming the agitation rate, in dpm, of the up and down for the inner tube inside the outer tube. On the up stroke, the bottom mesh in the inner tube moves upward to contact the product, and on the down stroke the product leaves the mesh and floats freely within the inner tube. Thus the action produced carries the product being tested through a moving medium.

There exist a few reports on the use of USP apparatus 3 for testing the drug release rate and comparing it to those obtained from the other methods[3-8] . However, most of these publications focus on extended-release dosage forms. The purpose of this report is to measure the dissolution of several IR products and to compare them to those obtained from USP apparatus 2 to examine whether USP apparatus 3 can be used as an alternative to USP apparatus 2.

MATERIALS AND METHODS

Materials

The choice of test drugs was based on their solubility according to the Biopharmaceutics Classification System[9] . Metoprolol is a highly soluble and highly permeable drug. Both ranitidine and acyclovir are poorly permeable and have a relatively high solubility. The fourth drug, furosemide, has a poor solubility. The tablet strengths for metoprolol, ranitidine, acyclovir, and furosemide were 100, 300, 800, and 80 mg, respectively. The other chemicals included potassium phosphate monobasic, hydrochloric acid, sodium acetate, sodium hydroxide, phosphoric acid, and glacial acetic acid. These chemicals were purchased from Sigma Inc and used as is. The reference standards were purchased from USP.

USP apparatus 2 (paddle)

The dissolution profiles of metoprolol tablets, acyclovir tablets, and ranitidine HCl tablets were studied using USP apparatus 2, in 900 mL of dissolution media, at rotation of 50 rpm, with a constant temperature bath at 37 ± 0.5°C. The dissolution media were 0.1 N HCl for metoprolol tablets, purified water for ranitidine tablets, 0.1 N HCl for acyclovir tablets, and pH 5.8 buffer for furosemide tablets. Four-milliliter samples were drawn at 5, 10, 15, 30, 45, and 60 minutes and replenished with 4 mL of fresh dissolution medium. The dissolution samples were filtered with a 0.45-µm nylon filter prior to analysis.

USP apparatus 3 (Bio-Dis)

The dissolution profiles studied with Vankel Bio-Dis 3 of metoprolol, acyclovir, ranitidine, and furosemide tablets were studied in 250 mL of dissolution media with a constant temperature bath at 37 ± 0.5°C. The mesh sizes for both top and bottom were 420 µm based on the report by Rohrs et al[7] . As with USP apparatus 2, the dissolution media were 0.1 N HCl for metoprolol tablets, purified water for ranitidine tablets, 0.1 N HCl for acyclovir tablets, and pH 5.8 buffer for furosemide tablets. The agitation intensities of the inner tubes used were 5, 15, and 25 dpm. Four-milliliter samples were drawn at 5, 10, 15, 30, 45, and 60 minutes and replenished with 4 mL of fresh dissolution medium. The dissolution samples were filtered with a 0.45 µm nylon filter prior to analysis.

Sample Analysis and Data Analysis

Sample analysis was carried out using ultraviolet spectrophotometer Beckman DU 7400. Samples were diluted with dissolution medium when necessary. All the standards were prepared from USP reference standards dissolved in appropriate dissolution media. The wavelengths used for analysis were 275 nm for metoprolol, 314 nm for ranitidine, 254 nm for acyclovir, and 274 nm for furosemide. The percentage of drug dissolved was calculated based on the concentrations of drugs. The dissolution profile comparison, when appropriate, was carried out using f_2 similarity factor[10] . The similarity factor is a logarithmic reciprocal square-root transformation of the sum of squared error and is a measurement of the similarity in the percentage of dissolution between the 2 curves:

$$f_2 = 50 \bullet \log\{[1 + (1/n)\sum (R_t - T_t)^2]^{-0.5} \bullet 100\} \quad (1)$$

Two dissolution profiles are considered similar when the f_2 value is greater than or equal to 50. Note that when both test and reference products dissolve 85% or more in no more than 15 minutes, the profile comparison with an f_2 test is unnecessary.

RESULTS

Dissolution of Metoprolol Tablets

Figure 1 shows the effect of the agitation rate on the dissolution of the innovator product of metoprolol. As expected, the dissolution rate increases with the increasing of the agitation rate. When the agitation rate reaches 15 dpm, further increase in agitation has little effect on the dissolution rate. The effect of the agitation rate on the dissolution of a generic product of metoprolol is shown in **Figure 2** . **Figure 2** confirms the observation that the higher the agitation rate the faster the tablet dissolves. However, unlike with the innovator product, with the generic product the agitation rate change from 15 to 25 dpm makes a significant difference in the dissolution rate. This suggests that the effect of the agitation rate on the dissolution rate depends on the formulation and manufacturing processes. These findings are consistent with the literature results obtained with the sustained-release dosage forms[7,8] .

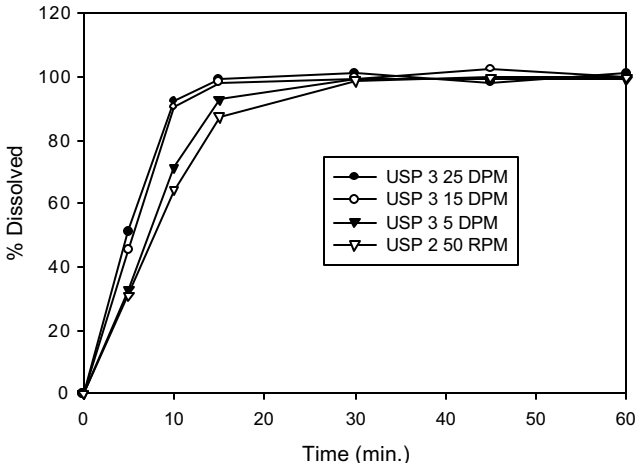

Figure 1. Dissolution profiles of metoprolol tartrate tablets of innovator's product.

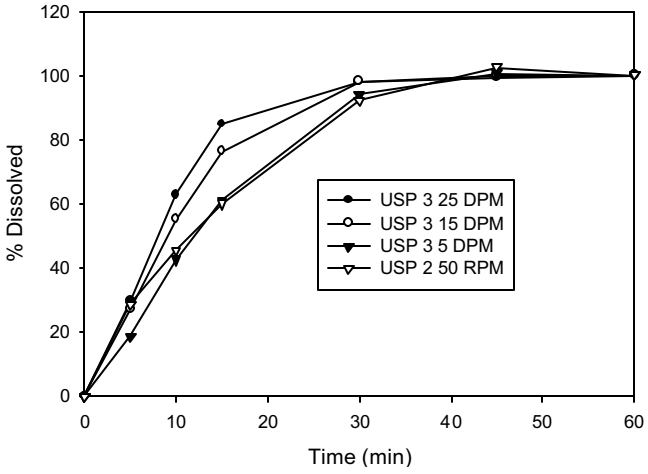

Figure 2. Dissolution profiles of metoprolol tartrate tablets of generic product A.

Figures 1 and **2** also show the dissolution profiles obtained with USP apparatus 2 at 50 rpm. It can be seen that the agitation rate of USP apparatus 3 should be around 5 dpm in order to provide dissolution profiles comparable to those from USP apparatus 2. Using the dissolution profiles from USP apparatus 2 at 50 rpm as a reference, the f_2 values for generic product A are 61, 50, and 38 for USP apparatus 3 at 5, 15, and 25 dpm, respectively. Thus, even at the agitation rate of 15 dpm, USP apparatus 3 produces similar dissolution profiles to USP apparatus 2, although USP apparatus 3 at 5 dpm offers even closer profiles to USP apparatus 2. These observations are in agreement with the finding in the literature for sustained-release dosage forms that the agitation rate giving hydrodynamic conditions equivalent to the 50 rpm paddle is at the extreme low end of the possible agitation rate range of 5 to 40 dpm of USP apparatus 3[7].

Dissolution testing was performed on 2 additional generic products B and C of metoprolol. The results are tabulated in **Table 1** along with the results from 3 lots of the innovator product and 1 lot of generic product A. In **Table 1** , we listed only the percentage dissolved at 10 minutes since it generally represents the most discriminating value to distinguish the dissolution profiles. **Table 1** shows that USP apparatus 3 at an appropriate agitation rate is able to generate formulation-specific dissolution profiles similar to those of USP apparatus 2.

Table 1. Percentage of Metoprolol Dissolved at 10 Minutes in 0.1 N HCl Using USP Apparatus 2 at 50 rpm and USP Apparatus 3 at 5 and 15 dpm.

Product	USP 2 (50 rpm)	USP 3 (5 dpm)	USP 3 (15 dpm)
Innovator, Lot A	73.6 ± 3.7	80.2 ± 3.9	93.9 ± 8.8
Innovator, Lot B	69.6 ± 3.1	71.4 ± 2.9	93.0 ± 11.8
Innovator, Lot C	82.4 ± 6.0	82.2 ± 4.7	88.0 ± 3.0
Generic A	47.2 ± 3.9	42.9 ± 5.0	56.9 ± 5.6
Generic B	61.8 ± 4.9	62.9 ± 3.2	83.0 ± 2.9
Generic C	41.5 ± 5.9	53.4 ± 2.0	80.5 ± 2.7

Dissolution of Ranitidine Tablets

Figures 3 and **4** show the dissolution profiles obtained from USP apparatus 2 at 50 rpm and USP apparatus 3 at the agitation rates of 5 and 15 dpm. It can be seen from **Figures 3** and **4** that the dissolution profiles from USP apparatus 3 are generally faster than those from USP apparatus 2. Unlike with the metoprolol tablets, even at the lowest agitation rate, 5 dpm, the dissolution of the ranitidine tablets with USP apparatus 3 is still faster than that with USP apparatus 2 at 50 rpm, especially at early time points.

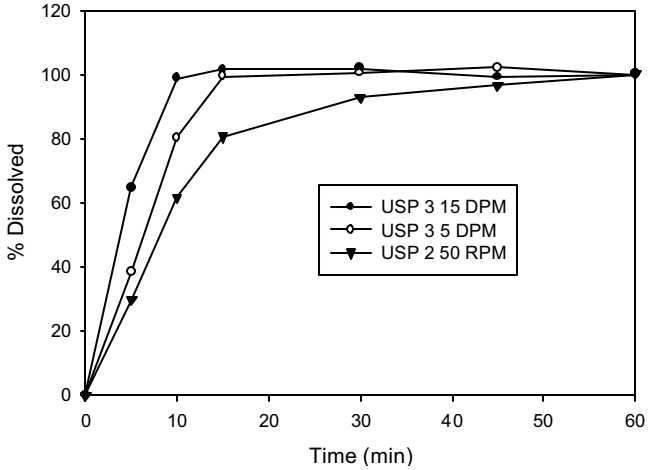

Figure 3. Dissolution profiles of ranitidine tablets of innovator's product.

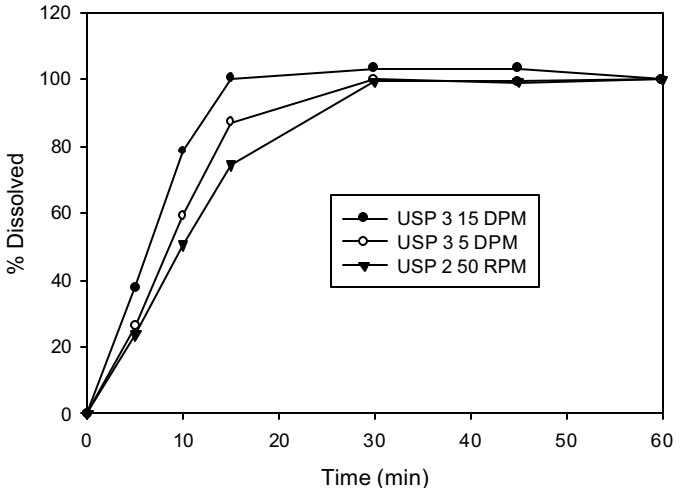

Figure 4. Dissolution profiles of ranitidine tablets of generic product A.

Among many factors influencing the choice of ranitidine products for evaluation was that many generic products failed to pass the dissolution profile comparison f_2 test although they were bioequivalent to the innovator product. For example, 2 out of 6 generic products we have tested failed the f_2 test based on USP apparatus 2 dissolution profiles. The discrepancy between in vivo and in vitro has 2 implications: either the f_2 test method is too conservative or the current in vitro dissolution does not mimic what is happening in vivo. A recent report showed that in vivo dissolution is much faster than that in vitro[11] . In fact, if USP apparatus 3 at 5 dpm were employed to evaluate the dissolution of ranitidine products, the f_2 would not even apply since the percentage dissolved at 15 minutes is above 85% for all ranitidine products, suggesting that these products are all bioequivalent. In this case, therefore, USP apparatus 2 seems overdiscriminating.

Table 2 shows the absolute differences between the innovator and generic products in the percentage dissolved at 10 minutes. The percentage dissolved at 10 minutes was chosen because it represents the most discriminating value to distinguish the difference between dissolution profiles. **Table 2** shows that USP apparatus 3 at 15 dpm is less discriminating while USP apparatus 3 at 5 dpm is equivalent to or more discriminating than USP apparatus 2 at 50 rpm. Therefore, USP apparatus 3 seems to perform at least as well as USP apparatus 2 in distinguishing the ranitidine dissolution characteristics in vitro.

Table 2. Absolute Difference of the Percentage Dissolved at 10 Minutes of Generic Products Against the Innovator Products using USP Apparatus 2 at 50 rpm and USP Apparatus 3 at 5 and 15 dpm.

Product	USP 2 (50 rpm)	USP 3 (5 dpm)	USP 3 (15 dpm)
Generic A	11.2	19.4	20.2
Generic B	9.4	19.6	2.1
Generic C	9.6	20.6	6.6
Generic D	29.1	19.8	2.8
Generic E	3.0	0.5	1.5
Generic F	16.1	8.0	1.3
Mean difference	13.1	14.8	5.75

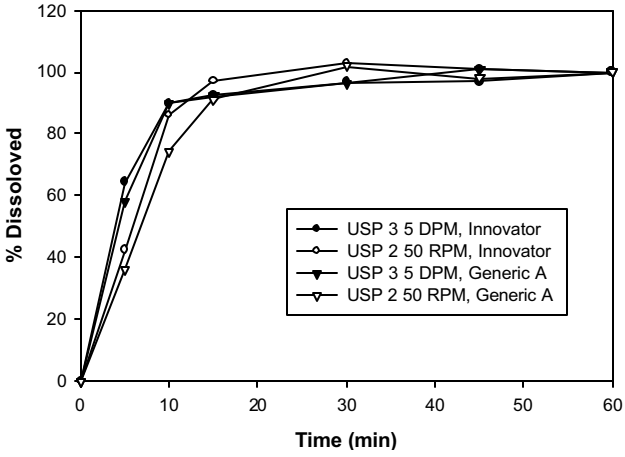

Figure 5. Dissolution profiles of acyclovir tablets of innovator and generic products.

Dissolution of Acyclovir Tablets

The dissolution testing of 6 acyclovir products (1 innovator and 5 generic products) was performed using both USP apparatus 2 and USP apparatus 3. **Figure 5** shows the dissolution results of the innovator and a typical generic product. The dissolution of all products is relatively fast, complete in 15 minutes. Both apparatuses produce similar results, with USP apparatus 3 producing a little bit more drug release at the early time points.

Dissolution of Furosemide Tablets

USP apparatus 3 was also used for the dissolution testing of furosemide tablets in the dissolution medium of pH 5.8 buffer. Furosemide is a low-solubility drug. It was found that not all drug particles dissolved during the testing period of 1 hour (data not shown). It is likely that the furosemide particles pass through the lower mesh and get into the bottom of the

outer tube, where agitation is not strong enough to have all the particles dissolve. This suggests that USP apparatus 3 may not be adequate for the dissolution of poorly soluble drugs dosed in IR dosage forms. Nevertheless, the recent modification[1] of the lower cap may resolve the inadequate agitation issues (data are not available on the modified apparatus). In addition, maintaining the sink conditions with the low-solubility drugs could be another issue, although this is not the case with the highly soluble drugs, such as metoprolol and ranitidine.

CONCLUSION

Although it is primarily designed for the release testing of extended-release products, USP apparatus 3 may be used for the dissolution testing of IR products for highly soluble drugs, such as metoprolol and ranitidine, and some IR products of poorly soluble drugs, such as acyclovir. It is shown that with appropriate agitation rate, USP apparatus 3 can produce similar dissolution profiles to USP apparatus 2 or distinguish dissolution characteristics to serve the purpose of product control. USP apparatus 3 certainly avoids the coning issues surrounding USP apparatus 2. Furthermore, it requires much less water and considerably fewer chemicals. If USP apparatus 3 can provide the function of automatic sampling, it is expected to be more efficient than USP apparatuses 1 and 2.

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